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The Wolff-Rearrangement Reaction of Oxidatively Generated α -Oxo Gold Carbenes: An Effective Approach to Silylketenes

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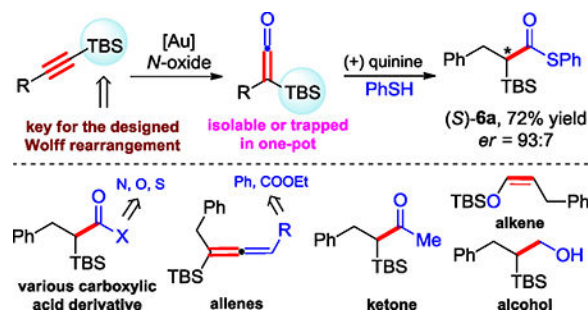
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Abstract

Gold-catalyzed oxidations of alkynes by *N*-oxides offer a direct access to reactive α -oxo gold carbene intermediates from benign and readily available alkynes instead of hazardous diazo carbonyl compounds. Despite various versatile synthetic methods developed based on this strategy, one of the hallmarks of α -oxo carbene/carbenoid chemistry, i.e., the Wolff rearrangement, has not been realized in this context. This study discloses the first examples that the Wolff rearrangement can be readily realized by α -oxo gold carbenes oxidatively generated from TBS-terminated alkynes. The thus-generated silylketenes can be isolated pure or subsequently trapped by various internal or external nucleophiles in one pot to afford α -silylated carboxylic acids, their derivatives or TBS-substituted allenes.

Graphical Abstract

The Wolff rearrangement is observed for the first time upon gold-catalyzed oxidation of terminally TBS-substituted alkyne. The silyl group is essential for this reaction, and the generated silylketenes are stable and can be isolated or subsequently trapped in a variety of manners to afford γ -lactones, α -silylated carboxylic acids and their derivatives, or silylallenes.



Keywords

the Wolff rearrangement; gold catalysis; α -oxo carbenes; silylketene; alkyne

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The Wolff rearrangement^[1] is one of the classical transformations of α -diazo ketones^[2] and has been extensively studied and widely employed in organic synthesis (Scheme 1A).^[3] The ketene generated in this powerful reaction is a reactive intermediate of exceptional synthetic value. The main drawback of the reaction, however, is the use of diazo ketone substrates, which are hazardous and potentially explosive but necessary to access highly reactive α -oxo carbene/carbenoid or undergo concerted conversion (Scheme 1A).

In 2010,^[4] we reported that highly electrophilic α -oxo gold carbene intermediates could be generated via intermolecular oxidation of benign alkynes instead of from hazardous diazo ketones (Scheme 1B).^[5] The safety benefit of this strategy and the new approach to α -oxo gold carbenes and their novel chemistry spurred a diverse range of subsequent studies by us^[4-5, 6] and others,^[7] which establish that the gold carbene intermediates or in some cases their precursors can undergo insertions into O-H,^[4, 6a] N-H,^[7j] B-H^[7i] and even unactivated C-H bonds,^[6f, 6g, 7a, 7d, 8] cyclopropanate alkenes^[6d, 6e, 7g, 7h] including electron-deficient ones,^[6e, 7g] electrophilic arene substitutions^[6c, 7e] or Buchner reaction,^[6h] and formation of ylides.^[7f, 9] Despite of these advances, no Wolff-type rearrangement involving these oxidatively generated α -oxo gold carbenes has been reported to date. Herein, we disclose a first example, which offers one-step access to stable yet versatile silyl ketenes from readily available TBS-terminated alkynes (Scheme 1C).

In 2015, we reported that acyl/acyl-substituted gold carbenes generated upon gold-catalyzed oxidation of enones undergo insertions into unactivated C-H bonds.^[6f] In our effort to expand the C-H insertion chemistry, we examined as substrates silyl-terminated alkynes including silylated 3-phenyl-1-propyne **1**. As shown in Table 1, entry 1, with the silyl group of **1** as TBS, IPrAuNTf₂ (5 mol %) as the catalyst and 8-isopropylquinoline *N*-oxide as the oxidant, the gold-catalyzed oxidation occurred smoothly overnight to deliver three identifiable products. Among them, the silylated indanone product **3** and its desilylated counterpart **2** were formed in 20% and <5% yield, respectively. The major product, formed in 75% NMR yield, is the α -silylated 3-phenylpropionic acid **5**. We realized that this compound must be formed upon the hydration of the corresponding silylketene **4**. This result suggests the Wolff rearrangement occurred in the process. Critical to the success of the oxidation is the NHC ligand, as a range of phosphine-based ones including PPh₃, JohnPhos, Mor-DalPhos, and BrettPhos were totally ineffective under the same reaction conditions (entry 2). Varying the catalyst counter anion from NTf₂⁻ to SbF₆⁻ (entry 3) or OTf⁻ (entry 4) led to a lower yield of **5**. Other *N*-oxides were screened as well. While the use of 8-methylquinoline *N*-oxide also resulted in a lower yield of **5** (entry 5), those based on pyridine, however, were completely ineffective for this reaction (entry 6). In an attempt to obtain the ketene intermediate **4**, 4 Å MS was added to the reaction to remove adventitious water. To our delight, the TBS ketene **4a** was indeed formed in 85% NMR yield and could be obtained upon column purification in 70% isolated yield (entry 7). Changing the TBS group in **1a** to smaller silyl groups such as TMS (entry 8), TES (entry 9) and Me₂PhSi (entry 10) led to the formation of desilylated indanone **2** in >90% yield but none of the corresponding **4** and **5** was detected, while the bulkier TIPS group led to little reaction (entry 11). When the conditions of entry 7 was applied to the silylated 4-phenylbut-1-yne (i.e., **1b**, entry 12), to our surprise, the reaction was sluggish, and only 20% NMR yield of the

expected silylketene **4b** was formed, while the rest of the starting material remained mostly unreacted. Upon further conditions optimization, it was found that increasing the catalyst loading to 10 mol % and introducing NaBARF₄ (10 mol %) as an additive significantly improved the substrate conversion to 89% (entry 13). The silylketene **4b** was obtained in 76% NMR yield and 60% isolated yields.

Silylketenes are isolable and valuable intermediates^[10] for organic synthesis.^[11] They are typically prepared via eliminations of α -silylated carboxylic acids^[12] and their derivatives,^[13] thermolysis of alkoxy-2-silylacetylenes,^[14] 1,3-silyl shift of (trimethylsiloxy)alkynes,^[11] and the Wolff rearrangement of α -diazo- α -silyl ketones.^[15] The common drawback of these approaches is inefficient access to the corresponding substrates, which may require lengthy routes, use hazardous materials and/or exhibit limited scope. For example, in the Rh-catalyzed Wolff rearrangement approach shown in the top half of Scheme 2,^[15b] four steps^[16] including the use of explosive diazomethane are necessary to deliver the silylketene product from phenylacetic acid. On the other hand, our oxidative gold catalysis offers a two-step and much safer route from likewise commercially available 3-phenylprop-1-yne (Scheme 2, the bottom half). Furthermore, in complicated molecule synthesis, a silyl group is usually employed as the terminal alkyne protecting group. As such, our approach to silyl ketenes would require only a single step. Notably, Rh- or Ru-catalyzed oxidative transformations of terminal alkynes to ketenes^[17] have been reported. However, this gold-catalysis produces stable silylketene, which could be isolated or subsequently react with nucleophiles including those incompatible with the metal catalyst, thereby offering much enhanced synthetic flexibility and potentially broader reaction scopes; moreover, the mechanism of this reaction is distinctively different from these studies, which involves Rh/Ru vinylidene intermediates.

With the optimized conditions in Table 1, entry 13, we then set out to explore the reaction scope. To avoid isolating ketene products, which sometimes closely elude with 8-isopropylquinoline, we opted to convert it directly to the corresponding thioester in a one-pot process, which can be done readily in the presence of 20% Et₃N as catalyst. As shown in Table 2, a phenyl group directly attached to or separated from the C-C triple bond by one or two methylene groups (entries 1–3) can be readily tolerated, and the α -silylthioesters were formed efficiently in each case. The phenyl group in entry 3 could be substituted with halogens (entries 4 and 5) or MeO (entry 6) or replaced with heteroaryls (entries 7 and 8) with little impact on the reaction efficiency. The exception is entry 4, where an *o*-F group led to a low substrate conversion (44%). Substrates with nonfunctionalized alkyl chain (entries 9–11) or various functionalized ones (entries 12–18) also reacted smoothly. Of particular note is that the sensitive THP-protected HO group in entry 15 is tolerated, suggesting the mild nature of the reaction. It is important to point out that the yields based on substrate conversion were uniformly high in all the cases. The low or moderate isolated yields in some entries are due to the incomplete substrate conversion. Our attempts to drive the reaction to completion by adding more catalyst, extending the reaction time and/or heating it at a higher temperature led to little improvement. It is possible that the silylketene product inhibits the gold catalysis.

Mechanistically, our ¹³C-labelling experiment (Eq. 1) established the alkyl/aryl migration instead of a silyl counterpart in this reaction.

intramolecular side reactions, thereby allowing the Wolff rearrangement to dominate. This rationale is consistent with the ineffectiveness of the smaller silyl groups (see Table 1, entries 8–10); c) a silyl group is known to offer less stability to an α -carbocation than a methyl group but more than a hydrogen^[20] and hence, the TBS group does not attenuate the reactivity of α -oxo gold carbenes to a significant extent.

In conclusion, we have discovered the first examples of the Wolff rearrangement by oxidatively generated α -oxo gold carbene species. The TBS group installed at the terminal alkyne is essential due to its steric shielding effect and electronic influence. The generated silylketenes are stable enough to be isolated or can be trapped by tethered HO groups or various external nucleophiles to afford γ -lactones, α -silylated carboxylic acid and their derivatives, or TBS-substituted allenes. The trapping by thiophenol is also realized asymmetrically. This strategy avoids the typical use of hazardous diazo ketone substrates and provides a facile one- or two-step route to synthetically versatile yet isolable silylketenes from readily available alkyne substrates. It is anticipated this chemistry would further advance the applications of silylketene in organic synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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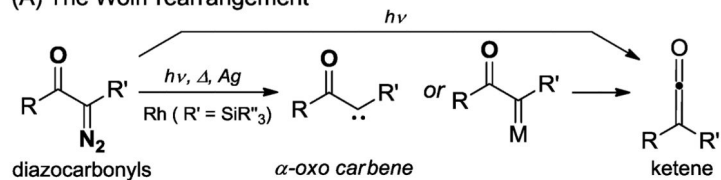
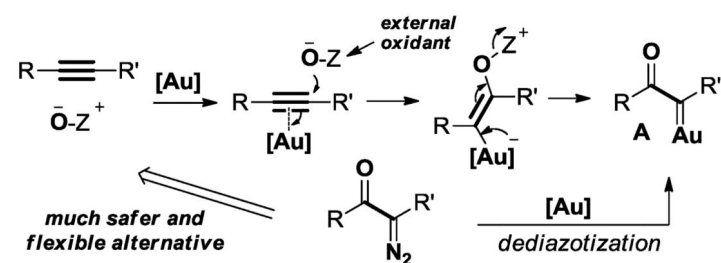
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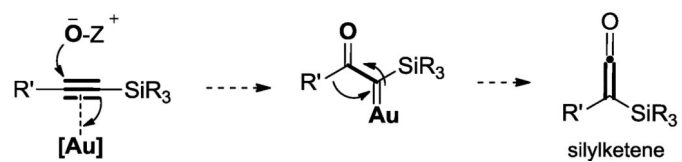
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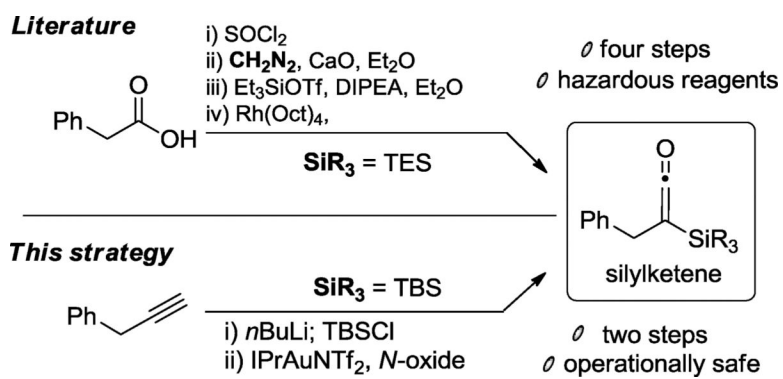
(A) The Wolff rearrangement

(B) Oxidative generation of α -oxo gold carbenes

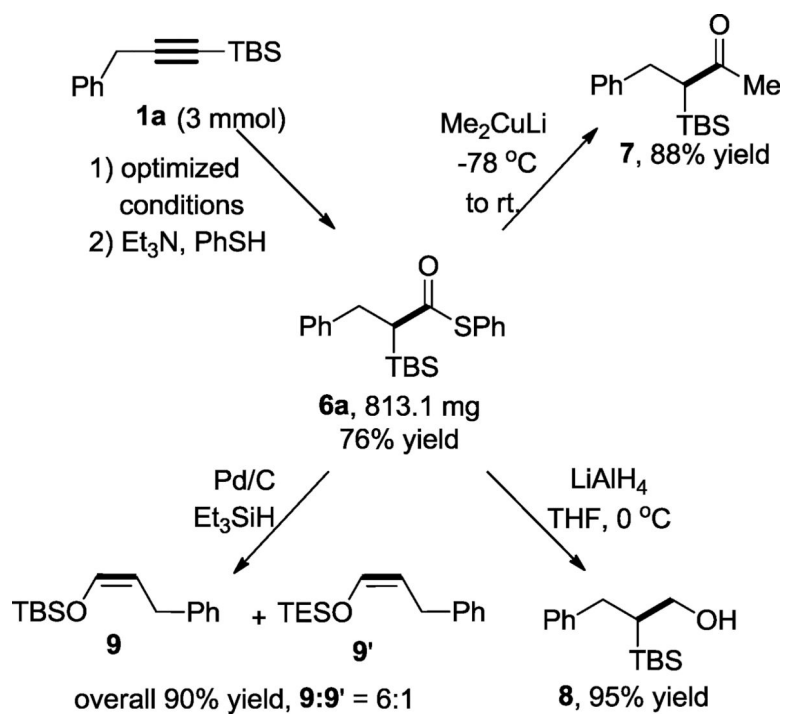
(C) This work:



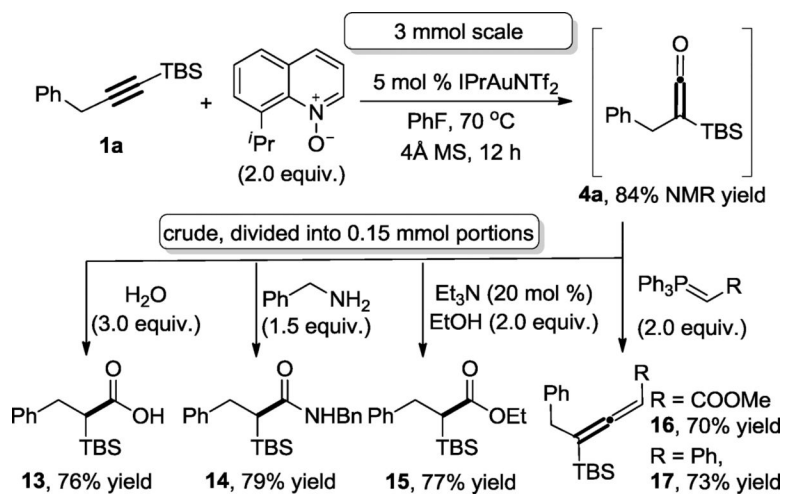
Scheme 1. The Wolff rearrangement and our design.



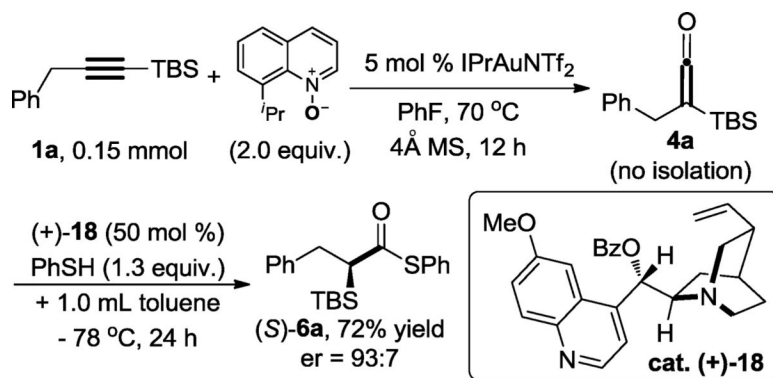
Scheme 2:
 Our strategy *versus* the reported.



Scheme 3.
Transformations of **6a**.

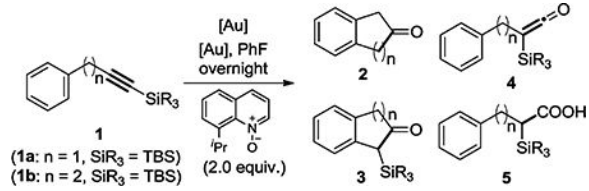
**Scheme 4.**

One-pot trapping the silylketene **4a** by various external nucleophiles.



Scheme 5.
Asymmetric trapping of the silylketene **1a**.

Table 1.

Reaction optimization. ^[a]


Reaction scheme showing the conversion of alkyne **1** to products **2**, **3**, **4**, and **5**. Reagents: [Au], [Au], PhF, overnight. Oxidant: 8-MeQNO (2.0 equiv.).

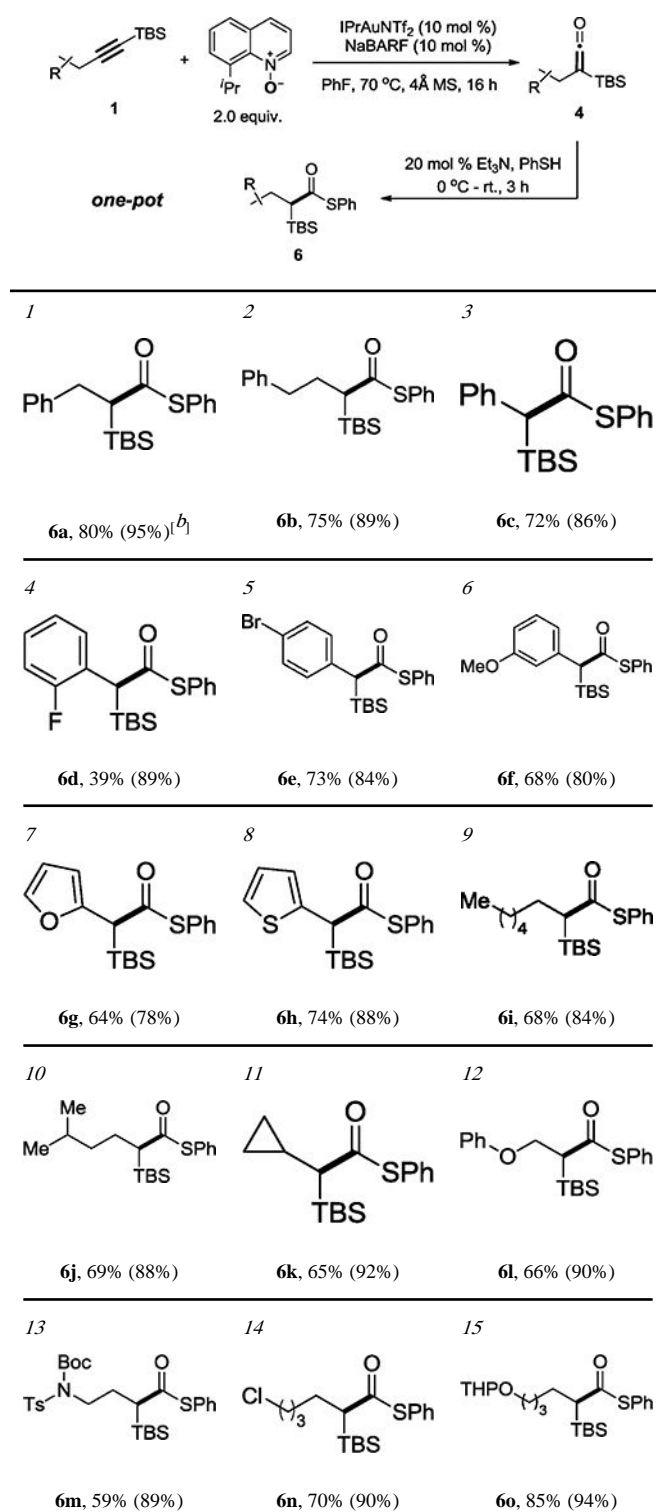
Substrate definitions:
1a: n = 1, SiR₃ = TBS
1b: n = 2, SiR₃ = TBS

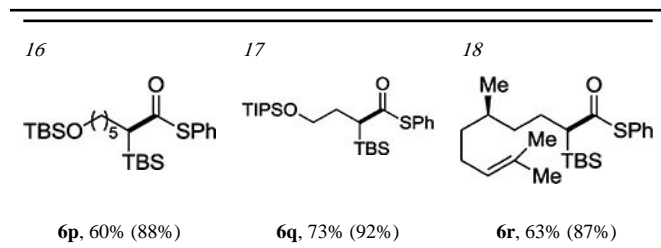
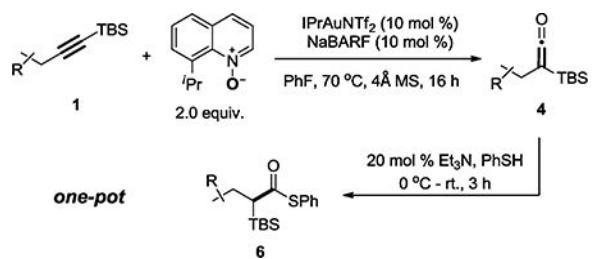
Entry	1 (n, SiR ₃)	conditions	Yield ^[b] (%)			
			2	3	4	5
1	1a (1, TBS)	IPrAuNTf ₂ (5%), 60 °C	<5	20	-	75
2	1a (1, TBS)	LAuNTf ₂ ^[c] (5%), 60 °C	NR ^[d]			
3	1a (1, TBS)	IPrAuCl/AgSbF ₆ (5%), 60 °C	<5	28	-	65
4	1a (1, TBS)	IPrAuCl/AgOTf (5%), 60 °C	<5	25	-	60
5	1a (1, TBS)	IPrAuNTf ₂ ^[e] (5%), 60 °C	-	35	-	55
6	1a (1, TBS)	IPrAuNTf ₂ ^[f] (5%), 60 °C	NR ^[d]			
7	1a (1, TBS)	IPrAuNTf ₂ (5%), 60 °C, 4 Å MS	-	10	85 ^[g]	<5
8	1-TMS (1, TMS)	IPrAuNTf ₂ (5%), 60 °C	>90	-	-	-
9	1-TES (1, TES)	IPrAuNTf ₂ (5%), 60 °C	>90	-	-	-
10	1-DMPS (1, SiMe ₂ Ph)	IPrAuNTf ₂ (5%), 60 °C	>90	-	-	-
11	1-TIPS (1, TIPS)	IPrAuNTf ₂ (5%), 60 °C	10	-	-	-
12	1b (2, TBS)	IPrAuNTf ₂ (5%), 60 °C, 4 Å MS	-	-	20	-
13	1b (2, TBS)	IPrAuNTf ₂ (10%), 70 °C, NaBARF (10%), 4 Å MS			76 ^[h]	

^[a]Initial [**1a**] = 0.05 M.^[b]NMR yields determined by using 1,3,5-trimethoxybenzene as the internal reference.^[c]L = PPh₃, JohnPhos, MorDalPhos, or BrettPhos.^[d]the remaining starting material.^[e]8-Methylquinoline *N*-oxide instead used as the oxidant.^[f]Various pyridine *N*-oxides as the oxidant.^[g]70% isolated yield.^[h]89% substrate conversion, and 60% isolated yield.

Table 2.

Substrate scope.





[a] Isolated yield reported, and yield based on substrate conversion given in parentheses.

[b] 5 mol % IPrAuNTf₂ and without NaBARF.